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The human brain response to dental pain relief

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Abstract

Local anesthesia has made dental treatment more comfortable since 1884, but little is known about associated brain mechanisms. Functional magnetic resonance imaging (fMRI) is a modern neuroimaging tool widely used for investigating human brain activity related to sensory perceptions, including pain. Recently, most brain regions that respond to experimental noxious stimuli have been found to react not only to nociception alone, but also to visual, auditory and other stimuli. Thus, presumed functional attributions have come under scrutiny regarding selective pain processing in the brain. Evidently, innovative approaches are warranted to identify cerebral regions that are nociceptive-specific. In this study, we aimed at circumventing known methodological confounders by applying a novel paradigm in 14 volunteers: rather than varying the intensity and thus the salience of painful stimuli, we applied repetitive noxious dental stimuli at constant intensity to the left mandibular canine. During the fMRI paradigm we suppressed the nociceptive barrage by a mental nerve block. Brain activity before and after injection of 4% articaine was compared intra-individually on a group level. Dental pain extinction was observed to correspond to activity reduction in a discrete region of the left posterior insular cortex. These results confirm previous reports demonstrating that direct electrical stimulation of this brain region - but not of others – evokes bodily pain sensations. Hence, our investigation adds further evidence to the notion that the posterior insula plays a unique role in nociceptive processing.

Introduction

In 1884, the Austrian ophthalmologist Carl Koller performed the first operation using local anesthetic on a patient with glaucoma (Koller, 1884). The news about the painless procedure spread rapidly across the globe (n.b. without internet), and in the same year American dentists were the first to use a syringe to apply infraorbital and mandibular nerve blocks (Hall, 1884). Considering the 130 year history of local anesthetics in dentistry remarkably little knowledge exists on their effects on the human brain. A meta-analysis recently summarized the relatively sparse evidence regarding the representation of experimental dental pain in the human brain (Lin et al., 2014). It revealed a cerebral network which mainly includes primary and secondary somatosensory cortices (S1 and S2), insula, thalamus, cingulate cortex and frontal brain regions. This dental pain network overlaps strongly with the neuromatrix (also referred to as “pain matrix”) reported for spinal pain (Iannetti and Mouraux, 2010). Compared to the latter, noxious tooth stimulation may gain an edge because of the extraordinary high proportion of nociceptive afferents in the dental pulp (Byers and Narhi, 1999; Chatrian et al., 1975). Yet, irrespective of stimulus type and location, pain related brain activity does not necessarily imply nociceptive specificity. Cumulating evidence indicates that brain regions responding to pain are equally involved in processing nociceptive and non-nociceptive stimuli (Iannetti and Mouraux, 2010; Mouraux et al., 2011). Hence, their activation may merely reflect

general responses to salient or behaviorally relevant stimuli, such as e.g. non-specific cognitive processes associated with magnitude estimation and/or motor aspects of pain intensity rating (Baliki et al., 2009). Since most pain studies performed categorical comparisons among different stimulus strengths, the functional distinction between salience and nociceptive related aspects of brain activity is precluded (Brugger et al., 2012; Coghill et al., 1999; Meier et al., 2012). Although efforts have been made to control for such effects, e.g. by means of advanced statistical modeling (Oertel et al., 2012), no experimental design has so far been able to unequivocally elucidate pain-specific effects within pain-associated brain regions.

Considering these conceptual challenges, the aim of this study was to develop an alternative approach by circumventing the various confounders of previous study designs. For this purpose we designed a novel functional magnetic resonance imaging (fMRI) paradigm that was based on keeping the dental noxious stimulus strength stable. To evoke pain perception contrasts, the barrage of nociceptive signaling was interrupted by an analgesic nerve block. Using this novel methodology, we hypothesized to 1) observe global dental pain related brain activations that replicate findings of previous neuroimaging studies and 2) to identify differential brain activity between the pain and analgesic states in distinct brain regions, reflecting the neuronal substrate underlying dental nociception.

Methods

Subjects

A total of 15 right-handed male subjects were recruited by advertising on an online platform (www.marktplatz.uzh.ch) and enrolled after informed written consent was obtained. One subject was excluded due to technical problems with the stimulation device, leaving a sample of 14 subjects (mean age = 25.14, SD = 4.48). Subjects were compensated with 50 Swiss francs per hour. The study was conducted according to the Declaration of Helsinki and was approved by the local ethics committee of the canton Zurich, Switzerland (KEK-ZH-Nr. 2012-0342).

Exclusion criteria included systemic diseases, history of allergy to the components of the local anesthetic solutions, local anesthesia in the mental region less than 2 weeks prior to the experiment, dental anxiety, acute or chronic pain condition, intake of analgesic medication. Further, on the target mandibular canine: dental sensitivity or caries, large restorations, or periodontal disease. Dental anxiety was assessed by the Dental Anxiety Scale (DAS) questionnaire (Corah, 1969). The mean DAS score was 6.29 (SD = 1.6). Alcohol was prohibited for 12 h before the experiment, and fMRI measurements were performed between 1 p.m. and 9 p.m.

Experimental Material

Dental splint

Mandibular splints were fabricated from impressions made of Blu-Mousse (Blu-Mousse is a fast-setting vinyl polysiloxane material produced by Parkell, Inc., 300 Executive Drive, Edgewood, NY 11717, USA) (Brugger et al., 2011; Brugger et al., 2012; Meier et al., 2014). Stainless steel electrodes were embedded in each splint at the labial and lingual centers of the left mandibular canine. They served as anode and cathode, respectively, during electrical stimulation of the tooth. To minimize electrical resistance during stimulation, a small portion of a specifically prepared contact hydrogel was placed on the anode and cathode. Care was taken that the splints did not evoke pain or discomfort.

Electrical stimulation

A modified “Compex Motion” system (Compex Médical SA, Ecublens, Switzerland) was used. This type of electrical stimulation system has been demonstrated to evoke reliable sharp and pricking pain sensations with minimal adaptive changes in sensory perception (Brugger et al., 2011; Brugger et al., 2012; Keller et al., 2002; Meier et al., 2014). The Presentation® software (<http://www.neurobs.com/presentation>) was used to control the experimental protocol. Shielded wires were used to avoid radiofrequency contamination by the stimulation current.

Local anesthetic

For the mental nerve block, a solution of 4% articaine (4-methyl-3-[2-(propylamino)-propionamido]-2-thiophene-carboxylic acid, methyl ester hydrochloride) containing 1:200,000 epinephrine was used (Ultracain D-S Forte®) which is currently the most common local dental anesthetic in Europe and has a long history of success (Cowan, 1977). Articaine blocks nociceptive input by binding reversibly to sodium channels and subsequently reducing sodium influx (Becker and Reed, 2012). Since small trigeminal fibers are generally more susceptible to local anesthetic solutions than thickly myelinated fibers, differential sensitivities are commonly observed in clinical dentistry as patients may remain disturbed by a sense of pressure despite complete analgesia (Becker and Reed, 2012).

Experimental procedure

Pretest 3-6 weeks prior to the fMRI experiment

Prior to the fMRI experiment, subjects were familiarized with the experimental procedure for minimizing arousal/anxiety effects and to secure a response to the local articaine 4%. Sensory detection threshold (SDT), pain detection threshold (PDT) and noxious stimulus intensity (NI; NRS 5/10) were individually determined by applying electrical stimuli of 1ms duration with increasing strength to the left lower canine (1mA steps; ascending method of limits). The NI was determined by increasing the stimulus strength until the subject rated a “5” (corresponding to a painful, but tolerable perception) on a verbally instructed 11-point numeric rating scale (NRS). The NRS left and right anchors were “no pain” and “worst pain imaginable”, respectively. Furthermore, pain quality was assessed by the verbal descriptors of “pricking,” “dull” and “pressing.” These three descriptors have

demonstrated discriminative properties to distinguish between A δ - and C-fiber-mediated pain (Beissner et al., 2010). 0.6 ml Articaine was subsequently injected at the left mental foramen according to the technique described by Schwenzer & Ehrenfeld (Schwenzer, 2009). Subject's analgesic responses were reported by indicating pain offset.

MR experiment

While subjects were lying in the MR scanner, SDT, PDT and NI were determined again by the ascending method of limits. Subjects were asked to indicate the SDT, PDT and NI by pressing the alarm bell of the MR system. All three threshold determinations (SDT, PDT and NI) were repeated thrice, and the mean current to achieve NI was applied during the subsequent stimulation.

In the pain phase, the lower left canine was stimulated 30 times at NI with randomized intervals of 8 to 12 s. For the purpose of the injection, the original MR scanner bed position was memorized by the MR system. To secure a constant brain position for both experimental phases, the subjects' head was immobilized in the MR coil by means of foamed cushions (Newmatic Medical, Caledonia, Michigan, USA) that filled the gap between coil and head. Additionally, participants were instructed to pay careful attention not to move their heads during scanner bed repositioning and the injection procedure, respectively. The articaine solution was submucosally injected above the left mental foramen. The injection procedure including the exact re-positioning of the scanner bed was kept below one minute. Thereafter, subjects continued receiving repetitive electrical stimuli at the NI level. The subjects were asked to report pain offset (complete analgesia) by pressing the MR alarm bell once and twice in case of nil stimulus perception (complete anesthesia).

Image acquisition

Functional and anatomical scans were obtained using a 3-T Phillips Ingenia scanner with a 15-channel receive-only head coil. A high-resolution T1-weighted anatomical image (field of view [FOV] = 22 cm, voxel size = 2.00 x 2.00 x 2.00 mm³, 170 slices) was first recorded for each subject. Thereafter, functional blood oxygenation level-dependent (BOLD) time series were recorded with a single-shot echo-planar imaging sequence (SENSE-sshEPI) to acquire 33 axial whole brain slices. The following acquisition parameters were used: echo time (TE) = 30 ms, repetition time (TR) = 2524 ms, FOV = 22 cm, acquisition matrix = 128 x 128, voxel size: 2.75 x 2.75 x 4.00 mm³, flip angle = 78° and SENSE acceleration factor R = 2.0. Using a mid-sagittal scout image, we placed 33 contiguous axial slices at 20-degree angles to the anterior-posterior commissure (AC-PC) plane, covering the whole brain. The pain phase consisted of 120 functional volumes whereas the post-injection phase consisted of 400 volumes.

Preprocessing

Preprocessing of functional brain images was conducted with the statistical parametric mapping

software SPM8 (Wellcome Department of Imaging Neuroscience, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/>). All volumes of the EPI sequence were corrected for slice timing, and subsequently, a spatial realignment to the first image in the series as a reference was performed. Subjects with detected movement that exceeded 2 mm (translational) or 1° (rotational) in relation to the reference were excluded. For studying the group effects, data were normalized to the MNI template brain using seven-degree B-spline interpolation followed by smoothing with a Gaussian kernel of 8 mm full-width-at-half-maximum (FWHM).

Statistical modeling and analysis

First- and second level statistics were performed with SPM8. A general linear model was used to partition the observed neuronal responses in components of interest, confounders and errors. An event-related analysis estimated the BOLD responses evoked by the potentially noxious stimuli by modeling them as delta function convolved with the canonical hemodynamic function as implemented in SPM8. In the first level analysis, all 30 noxious stimuli of the pain phase were modeled as a single regressor. In the post-injection phase, the first painful stimuli were implemented as regressors of no interest, whereas the first 30 stimuli after pain offset were implemented as regressors of interest. Furthermore, the motor task of pressing the alarm bell was modeled as regressors of no interest. Additional confounders were incorporated in each analysis within the design matrix, including the six rotational and translational parameters from the rigid body transformation, obtained during functional image realignment. Low-frequency fluctuations were removed with a high-pass filter (128 s). The serial autocorrelation of the BOLD time series was modeled using a first-order autoregressive model (AR[1]). The computed contrast maps derived from each subject were then entered into a random effects analysis.

To properly limit the amount of false positives, whole-brain topological inference using the false discovery rate method (FDR) based on Gaussian Random Field Theory was applied (Chumbley and Friston, 2009). The initial threshold for the subsequent cluster-based correction was set to $p < 0.001$. Only clusters that survived FDR correction were used for the interpretation of the results. One-sample t-tests for each of the two phases (pain and analgesic phase) were computed, see tables 1a and 1b. To account for possible brain activity induced by variations in the DAS questionnaire, DAS scores were implemented as covariates of no interest. Activations and deactivations associated with each regressor were tested by means of simple positive and negative t-contrasts. Within-group comparisons were performed by contrasting the pain and analgesic phase and vice versa in a paired t-test implemented in SPM8. Finally, the resulting voxel SPMt-maps were thresholded, color-coded and superimposed onto the avg152T1-MNI brain using xjview (<http://www.alivelearn.net/xjview8/>).

Results

Stimulus perception and pain relief

All subjects included in the final analysis reported a pricking pain experience during the entire pain phase, indicating predominantly A δ - fiber-mediated pain (Beissner et al., 2010). Following the articaine injection, pain stopped at 2.8 min (SD = 3.73 min). All subjects reported complete analgesia, but none experienced total anesthesia, as electrical stimuli were still perceived as a distinct non-painful (tap-like) sensation at the target tooth.

Brain activity results

Pain phase

The pain whole-brain analysis revealed responses in the left thalamus, left posterior insula, right anterior cingulate (pgACC, aMCC) and middle posterior cingulate (PCC), right inferior parietal, right superior temporal and left visual cortex, and right ventrolateral prefrontal cortex (VLPFC) ($p < 0.05$, FDR-corrected figure 1A, table1a).

Analgesic phase

The analgesic whole-brain analysis yielded activity in the left thalamus, right inferior parietal and left visual cortex, right VLPFC, left and right dorsolateral prefrontal cortex (DLPFC), left cerebellum and right hippocampus ($p < 0.05$, FDR-corrected figure 1C, table1b). Notably, no activity was found in the insular cortex.

Analgesic effects

The comparison between the pain and analgesic phase revealed a distinct and exclusive activation change within the left posterior insula, namely significantly reduced activity in the analgesic phase (Figure 1D, $p < 0.03$, FDR-corrected, cluster size = 60 voxels, peak MNI coordinate: -42 -8 2, $Z = 3.98$). The reverse contrast analgesic > pain phase revealed no significant results.

Discussion

The main findings of this study were that 1) global brain activations associated with dental pain as demonstrated in previous studies were replicated, except for lack of somatosensory activity and 2) differential brain activity between the pain and analgesic state was exclusively observed in the left posterior insula.

Pain is a conscious experience, modified by the interpretation of the nociceptive input and influenced by memories, emotional and cognitive factors (Tracey and Mantyh, 2007). Thus, studies using neuroimaging techniques (e.g. fMRI) are challenged with respect to their ability to isolate pain-specific brain responses, keeping in mind that the largest part of fMRI responses elicited by nociceptive stimuli reflects pain-unspecific processes. (Mouraux et al., 2011). The methodological novelty and particular strength of the present study is that many confounders were eliminated by

applying a constant and purely noxious stimulus to the tooth and subsequently blocking the nociceptive signaling by an articaine injection. The stimulus type selection was based on previous findings demonstrating that electrical dental pulp stimuli evoke sensory perceptions that are highly stable across time (Brown et al., 1985; Brugger et al., 2012; Meier et al., 2014). No pain rating was therefore required that could have caused blurring effects on fMRI findings due to cognitive and motor aspects of the rating. Further, the rationale behind selecting a tooth as a target site for a purely nociceptive stimulus is based on the fact that the tooth pulp is innervated primarily by nociceptive A δ - and C-fiber afferents (Baumgartner et al., 2012; Chatrian et al., 1975). This is also a likely reason why electrical tooth stimulation was one of the first models to evaluate pain specific evoked cortical potentials (Baumgartner et al., 2012; Van Hassel et al., 1972). The readily accessible mental nerve facilitates articaine injections. The times observed to pain offset are in line with other studies reporting pulpal anesthesia onsets and related inter-subject variability (Chumbley and Friston, 2009; Kambalimath et al., 2013).

Our findings of the pain phase correspond to results previously reported in dental pain neuroimaging studies with the exception of absent activity in somatosensory cortices (table 1a) (Brugger et al., 2012; Jantsch et al., 2005; Lin et al., 2014). Although a somatotopic S1 activation of different facial stimulation sites could be demonstrated (DaSilva et al., 2002), the meta-analysis of Lin et al. revealed inconsistent findings in this area as they reported a lack of S1 activity in 2 out of 6 studies (Lin et al., 2014), indicating that the response in this cortical area is less robust than in others. Peyron et al. interpret variability of S1 activation by its dependence 1) on the size of stimulation area and 2) stimulation frequency, i.e. by spatial and temporal summation phenomena (Peyron et al., 2000). These observations might also apply to our study as we used repetitive brief stimuli that were restricted to a single mandibular canine.

The contrast between the pain and analgesic states across all subjects revealed brain activity changes exclusive in a single brain region, namely the left posterior insula. This may not be immediately evident when looking at figure 1, where activations seemingly differ in various brain areas between the pain and analgesic phase. Yet the direct statistical comparison (paired-t-test) based on a whole-brain approach did not confirm such a finding.

The finding of significant activity changes solely in this area confirms cumulating evidence from other human reports which demonstrated that it is the most consistently activated area during acute pain perception (Duerden and Albanese, 2013; Garcia-Larrea, 2012; Oertel et al., 2012). In support of this observation, the posterior insula and adjoining medial parietal operculum are the only areas where direct electrical cortical stimulation triggered somatic pain in patients undergoing brain surgery (Mazzola et al., 2012). It is noteworthy that in a clinical study which included patients suffering from temporomandibular disorders, neurochemical changes in the left posterior insula have been observed (Gerstner et al., 2012).

By applying a conservative whole-brain statistical analysis with threshold of $p < 0.05$, corrected for multiple comparisons (FDR), the current investigation revealed a left-sided (ipsilateral) insular and thalamus activation during the pain phase. A more liberal statistical threshold of $p < 0.001$ uncorrected yielded bilateral activations in various brain regions (results not shown) which is in accordance with previous dental pain studies (Brugger et al., 2011; Cusick et al., 1986; Jantsch et al., 2005). Nevertheless, as we only stimulated and anesthetized a single tooth, a final answer about lateralization effects cannot be conclusively drawn.

Compared to other studies which also reported posterior insular activation, our functional cluster was located slightly more rostral (Garcia-Larrea, 2012; Henderson et al., 2011). In keeping with our results, the previously mentioned meta-analysis of dental neuroimaging studies demonstrated predominantly mid-insular activations (Lin et al., 2014). One might therefore speculate that there might be a somatotopic organization within the insular cortex as previously suggested (Mazzola et al., 2009).

As study limitations it must be noted that there is an absence of a standardized nociceptive stimulus in the field of pain studies. The pain model of the current study using brief electrical tooth stimulation characterizes acute pain of pulpal origin. As such it cannot be directly extrapolated to clinically-relevant pain induced by e.g. irreversible pulpitis, atypical odontalgia or trigeminal neuropathic pain (Baad-Hansen et al., 2008; Nixdorf et al., 2012). Further, estimation of statistical power was not possible due to a lack of prior data. We thus estimated that our sample size would offer sufficient power for identification of meaningful signal changes between the two experimental conditions, which indeed was observed.

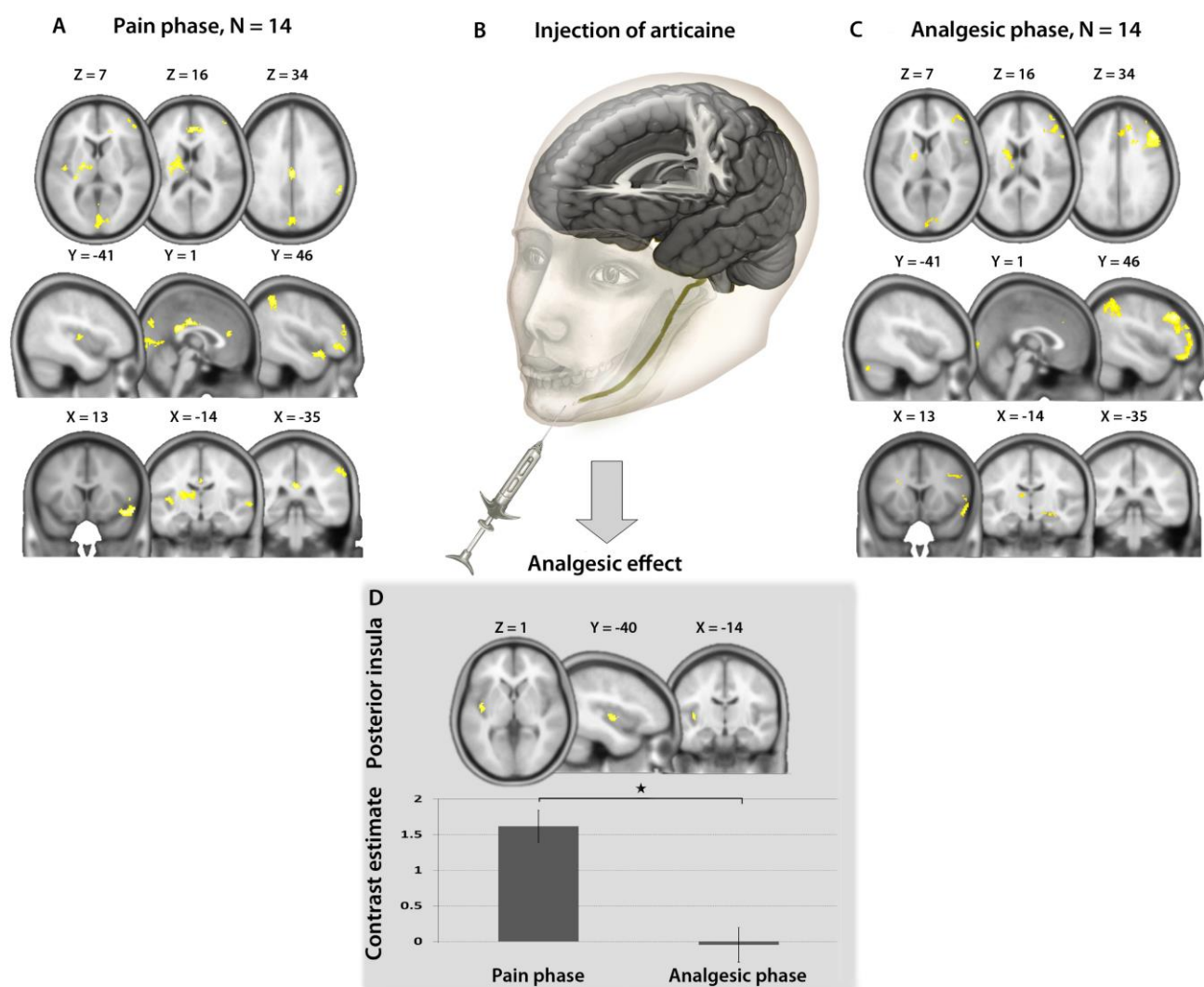
To conclude: the use of a peripheral nerve block to assess the human brain response to pain relief is a novel methodological approach. It can serve to better understand mechanisms that occur central to the injection of local anesthetics which for more than 130 years have been a cornerstone of dentistry and other areas of medicine. Our study results confirm and expand previous findings. Most importantly, the nociceptive specificity of the posterior insula as previously postulated based on direct cortical stimulation has been corroborated by a non-invasive technique, i.e. fMRI. Although fMRI has previously been employed for clarifying pain associated brain activity, our approach eliminated some important known confounders.

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Figures and Legends

Figure 1



Methods and results summary. Illustrated is the brain activity of the pain and analgesic phase during repetitive electrical stimulation. A: Whole-brain activity of noxious stimulation during the pain phase (one-sample t-test, $N = 14$, $p < 0.05$, FDR corrected). B: Site of injection of articaïne. C: Whole-brain activity of noxious stimulation during the analgesic phase (one-sample t-test, $N = 14$, $p < 0.05$, FDR corrected). D: Differential brain activity revealed by paired-t-test including the contrast “pain > analgesic phase”. Mean contrast estimates (and standard deviation of the mean \pm SD) of the respective posterior insular cluster are illustrated in the bar graph.

Table 1

Cluster maxima of brain activity with highest peaks (Z-score) ($p < 0.05$, false discovery rate corrected, FDR).

MNI = Montreal Neurological Institute, BA = Brodmann area, PCC = posterior cingulate cortex, STG = superior temporal gyrus, aMCC = anterior midcingulate cortex, pgACC = perigenual anterior cingulate cortex, IPL = inferior parietal lobe, DLPFC = dorsolateral prefrontal cortex, VLPFC = ventrolateral prefrontal cortex, OC = occipital cortex, LG = lingual gyrus

Noxious stimulation > baseline, pain phase (one-sample t-test, N = 14)

a	cluster size	q(FDR)	Z	MNI Peak coordinates			Brain region
	552	<0.001	4.30	62	-42	34	Right IPL (BA 40)
	245	<0.001	4.21	50	44	-2	Right VLPFC (BA 47)
	244	<0.001	4.08	0	-40	24	PCC (BA 23)
	286	<0.001	4.02	54	12	-12	Right STG (BA 38)
	194	<0.002	3.96	60	-6	2	Right STG (BA 41)
	511	<0.001	3.90	0	-98	-2	OC (BA 18)
	313	<0.001	3.89	-14	-12	10	Left Thalamus (BA 50)
	111	<0.02	3.86	14	38	16	Right ACC (pgACC, aMCC, BA 32)
	93	<0.04	3.70	-38	-12	0	Left insula (BA 13)
	156	<0.005	3.86	-24	-60	-2	Left LG (BA 19)
	111	<0.02	3.54	-2	-82	30	Left OC (BA 19)

Noxious stimulation > baseline, analgesic phase (one-sample t-test, N = 14)

b	cluster size	q(FDR)	Z	MNI Peak coordinates			Brain region
	673	<0.001	4.55	48	28	36	Right DLPFC (BA 9)
	508	<0.001	4.31	26	54	-12	Right VLPFC (BA 10)
	192	<0.001	4.17	-30	18	28	Left DLPFC (BA 9)
	562	<0.002	4.06	44	-54	54	Right IPL (BA 39)
	117	<0.001	4.04	-16	-58	-8	Left LG (BA 19)
	429	<0.002	3.88	-40	-78	-28	Left Cerebellum (declive)

109	<0.001	3.85	30	-18	-16	Right Hippocampus (BA 54)
195	<0.04	3.79	2	-96	2	Right OC (BA 18)
176	<0.005	3.78	-16	0	16	Left Thalamus (BA 50)
120	<0.03	3.75	56	14	-12	Left OC (BA 19)

pain > analgesic phase (paired t-test, N = 14)

c	cluster size	q(FDR)	Z	MNI Peak coordinates			Brain region
	60	<0.03	3.98	-42	-8	2	Left insula (BA 13)

analgesic > pain phase (paired t-test, N = 14)

d	cluster size	q(FDR)	Z	MNI Peak coordinates	Brain region
No significant results					

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